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# Premonitory symptoms in migraine: A cross-sectional study in 2714 persons

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## Abstract

**Aim:** To describe the frequency and number of premonitory symptoms (PS) in migraine, the co-occurrence of different PS, and their association with migraine-related factors.

**Methods:** In this cross-sectional study, a validated questionnaire was sent to Finnish migraine families between 2002 and 2013 to obtain data on 14 predefined PS, migraine diagnoses, demographic factors, and migraine characteristics. The estimated response rate was 80%.

**Results:** Out of 2714 persons, 2223 were diagnosed with migraine. Among these, 77% reported PS, with a mean number of 3.0 symptoms compared to 30% ($p < 0.001$) and 0.5 symptoms ($p < 0.001$) among 491 persons with non-migraine headaches. Yawning was the most commonly reported symptom (34%) among migraineurs. Females reported PS more frequently than males (81 versus 64%, $p < 0.001$) and experienced a higher number of different symptoms (mean 3.3 versus 1.8, $p < 0.001$). All measures of migraine severity were associated with a higher burden of PS. Light and sound sensitivity showed the highest co-occurrence (kappa = 0.51, 95% CI 0.47–0.55). In a generalized linear model, age, gender, higher frequency, duration and intensity of headache, reduced working capacity, most aura symptoms, and associated symptoms of the headache phase were significantly associated with an increased in the number of PS.

**Conclusion:** PS are experienced by a majority of migraineurs. More severe migraine is associated with a higher burden of PS. Since the material was not entirely representative of the general population of migraineurs, caution should be exercised in generalizing the results.

## Keywords

Headache, migraine, premonitory symptoms, aura

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## Introduction

Migraine is the most common neurological disease and is characterized by intermittent headache accompanied by nausea, vomiting, photophobia, and phonophobia (1). The premonitory symptoms (PS) of migraine are defined in the International Classification of Headache Disorders, 3rd edition (ICHD-III beta), as "symptoms preceding and

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forewarning of a migraine attack by 2–48 hours, occurring before the aura in migraine with aura and before the onset of pain in migraine without aura,'' with fatigue, elation, depression, unusual hunger, and craving for certain foods given as examples (1). However, various PS and timespans have been used in previous studies (2–8).

The pathophysiologic basis to the PS is incompletely understood, but the involvement of hypothalamic and dopaminergic mechanisms has been suggested (9,10). Recently, glyceryl trinitrate has been used to provoke migraine-like attacks as well as PS, allowing them to be studied directly, which might increase our insight into the pathophysiology of migraine (11,12).

Previous studies have reported that between 8% and 87% of adult migraineurs (4–7) and 67% of child migraineurs (8) experience PS. Varying study populations and definitions of PS might have contributed to the wide range of reported frequencies.

In a prospective study, it was shown that, in migraineurs with PS, the onset of headache attacks can be predicted several hours in advance (3). Early treatment guided by PS might be beneficial (13,14).

Our objectives were to determine the frequency and number of PS among persons from Finnish migraine families, to explore the co-occurrence of different PS, and to examine the association between PS and age, gender, and migraine characteristics.

## Methods

We employed a cross-sectional design, using the validated Finnish Migraine Specific Questionnaire for Family Studies (15), which was issued in connection to genetic studies, to obtain data on PS, migraine diagnoses, demographic factors, and migraine characteristics among migraineurs in Finnish migraine families.

Migraine patients seen by neurologists at outpatient headache clinics in six Finnish cities with at least three first-degree relatives with possible migraine were invited to participate in the study. Those who accepted received the validated questionnaire, as did their affected relatives and the first-degree relatives of any affected individual. The relatives, however, were not seen by a neurologist and had no physical examination.

The headache diagnoses were based on the ICHD criteria (1) for migraine and consisted of migraine without aura (MwoA) and migraine with aura (MwA), with the subtypes being typical aura with migraine headache, typical aura with non-migraine headache, typical aura without headache, and hemiplegic migraine. Headaches not fulfilling any of these criteria were denominated as non-migraine headaches. Participants were recruited between January 2002 and March 2013 and the study size was determined by the number of participants during this period ($n = 2714$).

The 14 predefined PS in the questionnaire were based on previous studies and selected according to consensus in the research group (Figure 1). The participants were asked if some of the symptoms repeatedly preceded the headache attacks without any specified time window, giving a binary response for every symptom. The questionnaire also covered headache frequency, duration and intensity, associated symptoms of the headache phase (unilaterality of headache, pulsating headache, aggravation by physical activity, nausea and/or vomiting, photophobia, and phonophobia), aura symptoms (photopsia, blurring of vision, visual field defect, scintillating scotoma, hemiparesis, hemisensory aura, and speech aura), and disability (working capacity and lifetime number of attacks requiring bed rest). Demographic factors consisted of age and gender. Age was divided into four groups for group analysis: 5–17, 18–40, 41–65, and above 65 years.

A composite variable, ''sum of associated symptoms'', was created by adding together the associated symptoms, forming groups of persons with 0–2, 3, 4, 5, and 6 symptoms. The outcomes were the frequency of PS (i.e. the proportion of persons that experienced at least one PS) and the total number of PS per person.

## Statistical analyses

Statistical analyses were performed using SPSS version 22.0.0. Numerical data were analyzed using the Kruskal–Wallis test and the Mann–Whitney $U$ test due to non-normality. Categorical data were analyzed using the $\chi^2$ test. The co-occurrence of PS was tested using Cohen's kappa with 95% confidence intervals (CI). A two-sided $p$-value $< 0.05$ was considered statistically significant. The p-values were not adjusted for multiplicity. In the case of missing data, the person was excluded from analyses involving that variable.

For the binary multiple logistic regression, we considered age, gender, self-rated working capacity, headache characteristics (frequency, duration, intensity, unilaterality, pulsating headache, nausea and/or vomiting, photophobia, and phonophobia), and aura symptoms to be valid predictors. The dependent variable was the presence of any PS. The following variables were not considered to be valid predictors: diagnosis, as their criteria were included in the analysis; aggravation by physical activity, due to the large number of missing data; and lifetime number of attacks requiring bed rest, in order to reduce the number of categorical variables. Non-significant predictors were removed one by one from the model, except for age and gender, which were kept to ensure adequate controlling for these variables. Multicollinearity was tested with a tolerance value threshold of 0.1. Correlations between predictors were tested using Spearman's rank

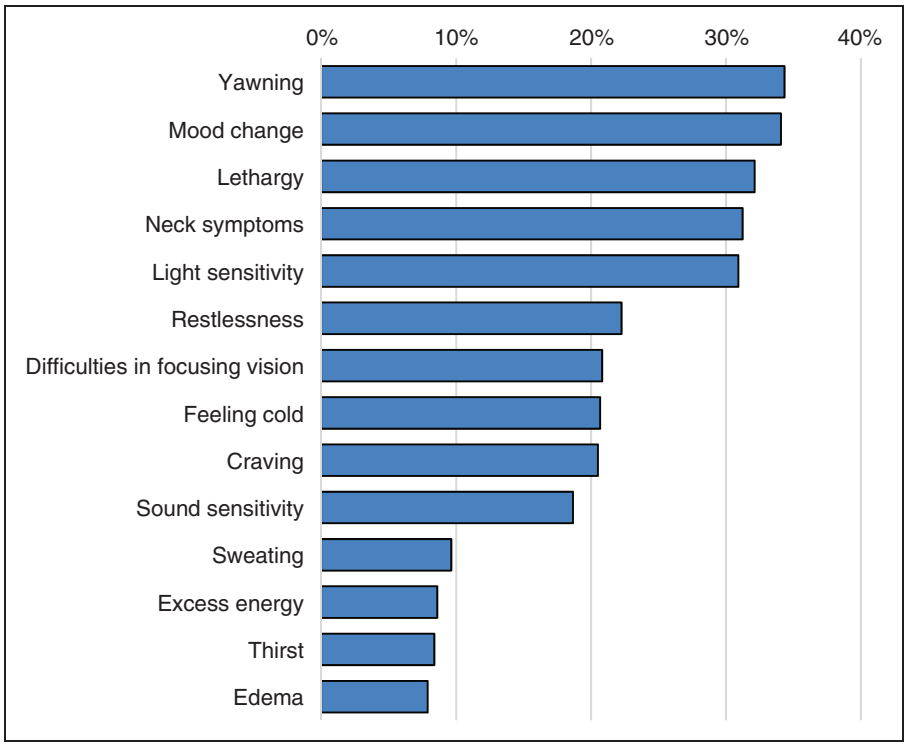


**Figure 1.** The frequency of individual premonitory symptoms among migraineurs ($n = 2219$).

correlation and only one of any strongly correlated ($r_s > 0.8$) predictors was included. Nagelkerke $R^2$ was used to evaluate the goodness of fit.

A generalized multiple linear model with a negative binomial distribution with a log link function was used for the regression analysis of the number of PS, as it was determined to be the best fit for our data that severely deviated from normality. Valid predictors were the same as for the logistic regression, as was the procedure for creating the model.

## Standard protocol approvals, registrations, and patient consent

The ethical committee of Helsinki University Central Hospital approved the study. The responders gave their informed consent to participate in the study. Each participant was assigned an individual identifier and the data were anonymized.

## Results

In total, data were collected from 2714 persons, of whom 2223 fulfilled different migraine criteria. Four persons received the diagnosis of typical aura without headache and were excluded from all analyses except for the comparison between migraine and non-migraine headaches. Thus, the migraine sample consisted of 2219 persons (475 males and 1744 females, mean age 45 years, SD 17, range 5–96), of whom 1188 fulfilled the MwA criterion and 1031 fulfilled the MwoA criterion. A total of 137 persons (62 males and 75 females) were aged 5–17 years (mean 13 years, SD 3). Of the 491 persons who had non-migraine headaches, 206 were males and 284 were females, with a mean age of 41 years (SD 20, range 6–88 years). We did not track the number of questionnaires sent out, but estimate that the number was 3400. As we received 2714 completed questionnaires, we estimate that the response rate was approximately 80%.

Among migraineurs, 77% reported one or more PS with a mean number of 3.0 (SD 2.9) different symptoms compared to 30% ($p < 0.001$) and 0.5 symptoms ($p < 0.001$) among those with non-migraine headaches (Table 1).

Yawning, mood change, and lethargy were the most common PS, each affecting about one third of all migraineurs (Figure 1).

Figure 2 shows the distribution of the number of symptoms experienced per person. Only 9% experienced more than seven PS (Figure 2).

Compared with persons with MwoA, those with MwA experienced PS slightly more frequently (79% *vs.* 75%) and reported a higher number of PS (mean 3.3 *vs.* 2.7) ($p < 0.05$) (Table 1). Among the subtypes of MwA, hemiplegic migraine was associated with the highest frequency (93%) and number of PS (mean 5.0), and typical aura with non-migraine headache

**Table 1.** Frequency and number of premonitory symptoms.

| Variable | Group | *n* | Frequency of premonitory symptoms (%) | *p*-value | Mean number of premonitory symptoms (SD) | *p*-value |
|---|---|---|---|---|---|---|
| Diagnosis | Any migraine | 2223 | 77 | | 3.0 (2.9) | |
| | nmHA | 491 | 30 | <0.001 | 0.5 (1.0) | <0.001 |
| Diagnosis | MwA | 1188 | 79 | | 3.3 (3.0) | |
| | MwoA | 1031 | 75 | 0.033 | 2.7 (2.7) | <0.001 |
| Sub-diagnosis | MwA1.2.1 | 824 | 82 | | 3.2 (2.8) | |
| | AwHA | 133 | 41 | | 0.8 (1.4) | |
| | HM | 231 | 93 | <0.001 | 5.0 (3.4) | <0.001 |
| Gender | Female | 1744 | 81 | | 3.3 (3.0) | |
| | Male | 475 | 64 | <0.001 | 1.8 (2.3) | <0.001 |
| Age | 5–17 | 137 | 71 | | 1.9 (2.0) | |
| | 18–40 | 730 | 77 | | 3.0 (2.9) | |
| | 41–65 | 1097 | 78 | | 3.2 (3.0) | |
| | >65 | 254 | 78 | 0.25 | 2.8 (2.8) | <0.001 |
| | Missing | 1 | | | | |
| HA frequency | <10 | 94 | 60 | | 1.6 (1.8) | |
| | 10–50 | 338 | 63 | | 1.7 (2.1) | |
| | 50–100 | 351 | 72 | | 2.2 (2.4) | |
| | >100 | 1425 | 83 | <0.001 | 3.6 (3.1) | <0.001 |
| | Missing | 11 | | | | |
| HA duration | <4 h | 354 | 62 | | 1.7 (2.0) | |
| | 4–72 h | 1554 | 79 | | 3.0 (2.8) | |
| | >72 h | 251 | 92 | <0.001 | 5.2 (3.2) | <0.001 |
| | Missing | 60 | | | | |
| HA intensity | Mild | 159 | 56 | | 1.5 (2.0) | |
| | Moderate | 780 | 73 | | 2.4 (2.5) | |
| | Severe | 980 | 81 | | 3.3 (2.9) | |
| | Unbearable | 294 | 88 | <0.001 | 4.6 (3.4) | <0.001 |
| | Missing | 6 | | | | |
| Working capacity | Normal | 335 | 58 | | 1.4 (1.8) | |
| | Working more difficult | 1230 | 80 | | 3.2 (2.9) | |
| | Not able to work | 604 | 84 | <0.001 | 3.7 (3.2) | <0.001 |
| | Missing | 50 | | | | |
| Attacks requiring bedrest | Never | 68 | 50 | | 1.1 (1.5) | |
| | <5 | 213 | 60 | | 1.6 (2.0) | |
| | 5–10 | 296 | 68 | | 1.9 (2.1) | |
| | 10–50 | 412 | 71 | | 2.0 (2.2) | |
| | 50–100 | 415 | 84 | | 3.3 (2.8) | |
| | >100 | 640 | 89 | <0.001 | 4.4 (3.2) | <0.001 |
| | Missing | 175 | | | | |
| Unilaterality of HA | Yes | 1484 | 82 | | 3.4 (3.0) | |
| | No | 661 | 68 | <0.001 | 2.2 (2.6) | <0.001 |
| | Missing | 74 | | | | |
| Pulsating HA | Yes | 1235 | 80 | | 3.2 (2.9) | |
| | No | 876 | 75 | 0.011 | 2.8 (2.9) | <0.001 |
| | Missing | 108 | | | | |
| Aggravation by physical activity | Yes | 1639 | 82 | | 3.4 (3.0) | |

(continued)

**Table 1.** Continued.

| Variable | Group | *n* | Frequency of premonitory symptoms (%) | *p*-value | Mean number of premonitory symptoms (SD) | *p*-value |
|---|---|---|---|---|---|---|
| | No | 252 | 67 | <0.001 | 2.0 (2.4) | <0.001 |
| | Missing | 328 | | | | |
| Nausea/vomiting | Yes | 1989 | 79 | | 3.2 (2.9) | |
| | No | 202 | 61 | <0.001 | 1.4 (1.9) | <0.001 |
| | Missing | 28 | | | | |
| Photophobia | Yes | 2094 | 79 | | 3.1 (2.9) | |
| | No | 106 | 56 | <0.001 | 1.1 (1.5) | <0.001 |
| | Missing | 19 | | | | |
| Phonophobia | Yes | 1886 | 82 | | 3.3 (2.9) | |
| | No | 285 | 54 | <0.001 | 1.2 (1.7) | <0.001 |
| | Missing | 48 | | | | |
| Sum of associated symptoms | 0–2 | 54 | 50 | | 0.8 (1.0) | |
| | 3 | 134 | 66 | | 1.8 (2.5) | |
| | 4 | 290 | 71 | | 2.1 (2.5) | |
| | 5 | 666 | 81 | | 3.3 (2.9) | |
| | 6 | 615 | 90 | <0.001 | 4.2 (3.0) | <0.001 |
| | Missing | 460 | | | | |

nmHA: non-migraine headache; MwA: migraine with aura; MwoA: migraine without aura; AwHA: typical aura with non-migraine headache; HM: hemiplegic migraine; MwA1.2.1: typical aura with migraine headache; HA: headache; associated symptoms: unilaterality of headache, pulsating headache, aggravation by physical activity, nausea and/or vomiting, photophobia, and phonophobia.

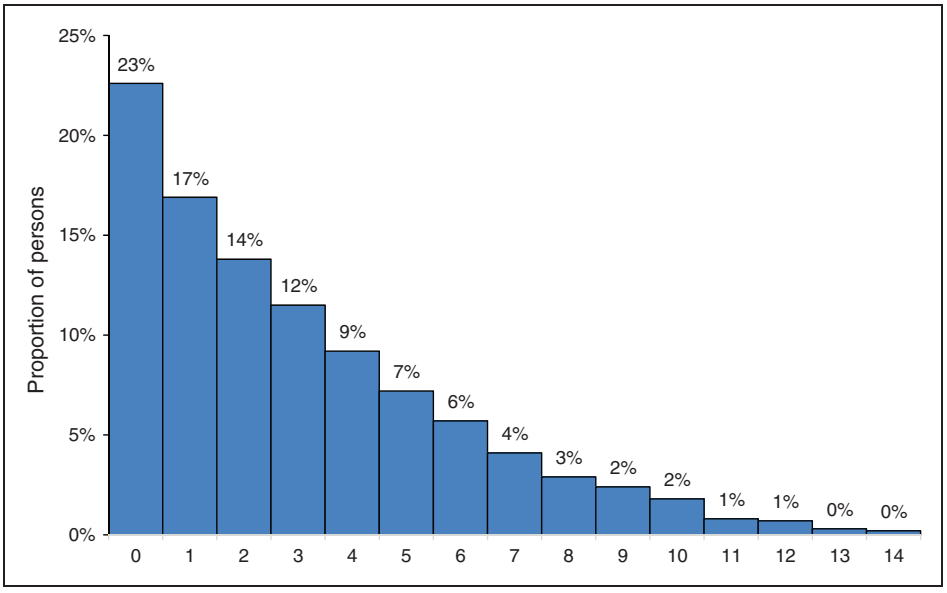


**Figure 2.** The number of premonitory symptoms experienced per person among migraineurs ($n = 2219$).

was associated with the lowest frequency and number of PS (41%; mean 0.8) ($p < 0.001$). Females reported PS more frequently and with a higher number of different symptoms than males (Table 1). The frequency of PS in different age groups did not differ significantly ($p = 0.25$), but the difference in the number of different symptoms was significant, being the lowest in the 5–17 age group.

**Table 2.** Kappa coefficients for the co-occurrence of premonitory symptoms ($n = 2219$).

| | EE | RS | CG | TT | YG | MC | DF | LY | LS | SS | FC | SG | EA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Excess energy (EE) | | | | | | | | | | | | | |
| Restlessness (RS) | 0.19 | | | | | | | | | | | | |
| Craving (CG) | 0.21 | 0.22 | | | | | | | | | | | |
| Thirst (TT) | 0.13 | 0.15 | 0.16 | | | | | | | | | | |
| Yawning (YG) | 0.14 | 0.26 | **0.36** | 0.11 | | | | | | | | | |
| Mood change (MC) | 0.17 | **0.39** | 0.29 | 0.12 | **0.33** | | | | | | | | |
| Difficulties in focusing vision (DF) | 0.09 | 0.25 | 0.13 | 0.14 | 0.16 | 0.17 | | | | | | | |
| Lethargy (LY) | 0.15 | 0.22 | 0.27 | 0.14 | **0.42** | 0.30 | 0.15 | | | | | | |
| Light sensitivity (LS) | 0.10 | 0.21 | 0.17 | 0.09 | 0.17 | 0.25 | 0.25 | 0.21 | | | | | |
| Sound sensitivity (SS) | 0.17 | 0.29 | 0.24 | 0.11 | 0.22 | 0.30 | 0.27 | 0.25 | **0.51** | | | | |
| Feeling cold (FC) | 0.17 | 0.24 | 0.27 | 0.16 | **0.31** | 0.25 | 0.16 | **0.31** | 0.18 | 0.21 | | | |
| Sweating (SG) | 0.15 | 0.22 | 0.10 | 0.22 | 0.14 | 0.16 | 0.14 | 0.16 | 0.14 | 0.19 | 0.19 | | |
| Edema (EA) | 0.16 | 0.14 | 0.19 | 0.20 | 0.15 | 0.16 | 0.11 | 0.12 | 0.10 | 0.16 | 0.15 | 0.18 | |
| Neck symptoms | 0.13 | 0.20 | 0.22 | 0.08 | 0.22 | 0.23 | 0.12 | 0.23 | 0.16 | 0.16 | 0.17 | 0.11 | 0.13 |

The highest values are shown in bold.

Higher levels of headache frequency, headache duration, headache intensity, working capacity, and lifetime number of attacks requiring bed rest were all associated with a higher frequency and number of PS (Table 1).

All of the associated symptoms of the headache phase (unilaterality of headache, pulsating headache, aggravation by physical activity, nausea and/or vomiting, photophobia, and phonophobia) were individually associated with a higher frequency and number of PS (Table 1). When adding together the associated symptoms, the frequency and number of PS increased with the number of symptoms.

The PS with the highest co-occurrence were light and sound sensitivity (kappa = 0.51, 95% CI 0.47–0.55), yawning and lethargy (kappa = 0.42, 95% CI 0.38–0.46), as well as mood change and restlessness (kappa = 0.39, 95% CI 0.35–0.43) (Table 2).

In the binary logistic regression, age, headache duration, headache intensity, unilaterality, phonophobia, photopsia, blurring of vision, hemisensory aura, and speech aura were associated with an increased probability of the presence of any PS, while scintillating scotoma was associated with a decreased probability of the presence of any PS (Table 3). Age increased the odds of experiencing PS by 1.0% (95% CI 0.3–1.7%) per year ($p = 0.005$). Gender was not significantly associated with the presence of PS. The model was significant when tested against a constant-only model ($\chi^2(14) = 289.3$, $p < 0.001$). The correct prediction rate was 79.4% (96.5% for the presence and 16.5% for the absence) compared to 78.6% for the constant-only model. Nagelkerke $R^2$ was 0.213. Due to missing observations, 1959 valid observations were used in the analysis.

In the generalized linear model, age, gender, headache frequency, headache duration, headache intensity, working capacity, unilaterality, nausea and/or vomiting, phonophobia, photopsia, blurring of vision, hemisensory aura, and speech aura were associated with an increased number of PS, while scintillating scotoma was associated with a decreased number of PS (Table 3). For instance, age increased the number of PS by 0.5% (95% CI 0.3–0.7%) per year ($p < 0.001$). The model was significant when tested against the null model (likelihood ratio $\chi^2(21) = 756.5$, $p < 0.001$, deviance/df = 1,21). Due to missing observations, 1911 valid observations were used in the analysis.

## Discussion

This study is, to date, the largest study of PS, including altogether 2714 persons with headache. The frequency of PS of 77% among migraineurs in this material is within the previously reported range of 8–87% (4–7), comparable to the frequency found in 100 persons seeking a general practitioner for migraine headache (84%) (5) and 374 migraine patients from a neurology outpatient clinic (87%) (7), but higher than in a study of 484 migraineurs in the general population (8%) (4) and 893 at a tertiary care clinic (33%) (6). Among the 137 persons below 18 years of age, the frequency of PS was 71%, which is in line with a previous report of 67% in 103 pediatric–adolescent migraine patients (8). The mean number of different PS per person of 3.0 out of a possible 14 is similar to a previously reported mean of 3.2 symptoms out of 12 (7).

The most commonly reported individual symptoms in the present study, namely yawning, mood changes,

**Table 3.** Predictors in the regression analyses.

| Predictor | Odds ratio[a] (95% CI) | *p*-value | EXP (b) (95% CI) | *p*-value |
|---|---|---|---|---|
| Age | 1.010 (1.003–1.017) | 0.005 | 1.005 (1.003–1.007) | <0.001 |
| Gender, female | 1.28 (0.98–1.69) | 0.076 | 1.16 (1.04–1.29) | <0.007 |
| Headache frequency | [c] | | | <0.001 |
| <10 | [c] | | 0.76 (0.59–0.96) | 0.024 |
| 10–50 | [c] | | 0.74 (0.65–0.84) | <0.001 |
| 50–100 | [c] | | 0.82 (0.73–0.91) | <0.001 |
| >100 | [c] | | 1.00 (reference) | |
| Headache duration | | 0.002 | | <0.001 |
| <4 h | 0.69 (0.51–0.93) | 0.015 | 0.86 (0.75–0.98) | <0.021 |
| 4–72 h | 1.00 (reference) | | 1.00 (reference) | |
| >72 h | 1.83 (1.08–3.08) | 0.024 | 1.30 (1.17–1.44) | <0.001 |
| Headache intensity | | 0.032 | | <0.003 |
| Mild | 0.59 (0.38–0.92) | 0.021 | 0.83 (0.68–1.02) | 0.074 |
| Moderate | 0.83 (0.64–1.08) | 0.165 | 0.92 (0.84–1.00) | 0.060 |
| Severe | 1.00 (reference) | | 1.00 (reference) | |
| Unbearable | 1.29 (0.82–2.01) | 0.268 | 1.19 (1.07–1.32) | <0.002 |
| Working capacity | [c] | | | <0.013 |
| Normal | [c] | | 0.78 (0.68–0.90) | <0.001 |
| Working more difficult | [c] | | 1.00 (reference) | |
| Not able to work | [c] | | 0.94 (0.86–1.03) | 0.179 |
| Unilaterality | 1.38 (1.07–1.77) | 0.012 | 1.10 (1.00–1.20) | 0.046 |
| Nausea and/or vomiting | [c] | | 1.35 (1.15–1.59) | <0.001 |
| Photophobia | [c] | | 1.23 (0.96–1.58) | 0.097 |
| Phonophobia | 2.30 (1.71–3.10) | <0.001 | 1.61 (1.38–1.87) | <0.001 |
| Scintillating scotoma | 0.73 (0.57–0.94) | 0.015 | 0.91 (0.84–0.98) | 0.015 |
| Photopsia | 1.63 (1.21–2.20) | 0.001 | 1.24 (1.14–1.34) | <0.001 |
| Blurring of vision | 1.64 (1.18–2.27) | 0.003 | 1.14 (1.05–1.24) | 0.002 |
| Hemisensory aura | 1.81 (1.31–2.51) | <0.001 | 1.17 (1.08–1.28) | <0.001 |
| Speech aura | 2.21 (1.54–3.17) | <0.001 | 1.53 (1.40–1.67) | <0.001 |

[a]Logistic regression ($n = 1959$).
[b]Generalized linear model ($n = 1911$).
[c]Not included in the model.
[d]Exp (b) is the exponent.

lethargy, neck symptoms, and light sensitivity, have all previously been shown to be frequent, with some variation between studies (3,5–8).

As expected, PS were more than twice as common in migraine headaches as in non-migraine headaches. Persons with MwA reported PS significantly more often and experienced a higher number of PS compared to those with MwoA, which has not been reported previously (4,5,7,8). The differences were much larger between the subtypes of MwA, with hemiplegic migraine having by far the highest frequency and number of PS. This is in agreement with hemiplegic migraine being at the very end of the spectrum of migraine severity.

Sound and light sensitivity showed the highest co-occurrence, which might represent a common origin, as both symptoms are aspects of sensory hypersensitivity. Yawning showed a high co-occurrence with several other symptoms; for instance, lethargy, craving, and mood changes. In a previous study exploring co-occurrences of PS, associations between these symptoms were not as strong as those between depression and irritability, concentration problems, and fatigue (7).

All measures of severity (frequency, duration, intensity, working capacity, attacks requiring bed rest, and presence of associated symptoms) were related to a higher burden of PS. This is in accordance with clinical impressions and previous findings that severe pain is associated with a higher number of PS than mild–moderate pain (5) and that those who experience PS have a longer duration of headache and more nausea (i.e. more

is more in migraine) (6). These factors also significantly and greatly affected the PS as predictors in the regression analyses. An unpredicted exception was that scintillating scotoma was associated with a lesser burden of PS.

In this material, a relatively large number of participants reported a typical headache duration of less than 4 hours. This may be due to the large number of children (in whom a shorter duration is more common) (16), the effects of successful treatment, or the uncertainty of self-reported time estimates. In addition, the ICHD criteria for MwA do not include a minimum duration (1).

The number of PS differed across age groups and age was a significant predictor in both regression analyses. Previously, in smaller studies, age has not been associated with PS (5,7,8).

As in this study, females have been associated with a higher number of PS previously (7), while there have been no gender differences in other studies (4–6,8). In the generalized linear model, females reported a 16% higher number of PS. Females have a higher prevalence of migraine and more severe migraines than males (17), thus our findings might be explained by a stronger migraine phenotype in females.

Strengths of the study include the vast material, the large pediatric–adolescent subset, and ample information on other characteristics of the migraines.

In terms of the limitations of the study, firstly, the material did not represent the general population because the questionnaire was only distributed to migraine patients and their relatives. While the study population did consist of persons from a wide range of ages with both genders being well represented, our sampling strategy caused the material to be skewed towards those with a larger hereditary burden and more severe migraine, which was shown in that MwA was more common than MwoA and in that hemiplegic migraine was considerably more prevalent than expected, at approximately one-tenth of all migraineurs compared to an estimated 1 in 10,000 in the general population (18). However, this allowed us to study the relationship between PS and measurements of migraine severity across their entire range.

Secondly, retrospective questions have the drawback of potential recall bias and lack the prospective recordings of the frequency and temporal aspects of the symptoms. We did not determine the frequency of the symptoms we considered to be PS during headache-free intervals, which is more readily done with a prospective approach, and this might have led to an overestimation of their rate, as several such symptoms have been shown also to be common outside the migraine attack (5).

Furthermore, all of the PS in the study were predefined, which could result in a lower reported frequency than with open questions in which participants are able to add their other observed symptoms. For instance, ''face changes'', which in a previous report was the most common individual PS among children, was not included (8). However, open questions might have introduced unspecific symptoms and been unfavorable for determining co-occurrences.

In conclusion, PS are experienced by a majority of migraineurs, more commonly in females. A higher burden of PS is associated with a more severe migraine. Thus, further understanding of the pathophysiology of the premonitory phase is desired to enable the development of specific therapy for this early phase of migraine that might alleviate the subsequent attack.

## Clinical implications

- Increased knowledge of the occurrence of premonitory symptoms (PS) could help in understanding the pathophysiologic basis of migraine.
- Among 2223 individuals with migraine, 77% reported PS.
- More severe migraine was associated with a higher burden of PS.

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## References


1. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013; 33: 629–808.
2. Houtveen JH and Sorbi MJ. Prodromal functioning of migraine patients relative to their interictal state – an ecological momentary assessment study. *PLoS One* 2013; 8: e72827.
3. Giffin NJ, Ruggiero L, Lipton RB, et al. Premonitory symptoms in migraine: an electronic diary study. *Neurology* 2003; 60: 935–940.
4. Russell MB, Rasmussen BK, Fenger K, et al. Migraine without aura and migraine with aura are distinct clinical entities: a study of four hundred and eighty-four male and female migraineurs from the general population. *Cephalalgia* 1996; 16: 239–245.
5. Quintela E, Castillo J, Munoz P, et al. Premonitory and resolution symptoms in migraine: a prospective study in 100 unselected patients. *Cephalalgia* 2006; 26: 1051–1060.
6. Kelman L. The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs. *Headache* 2004; 44: 865–872.
7. Schoonman GG, Evers DJ, Terwindt GM, et al. The prevalence of premonitory symptoms in migraine: a questionnaire study in 461 patients. *Cephalalgia* 2006; 26: 1209–1213.
8. Cuvellier JC, Mars A and Vallee L. The prevalence of premonitory symptoms in paediatric migraine: a questionnaire study in 103 children and adolescents. *Cephalalgia* 2009; 29: 1197–1201.
9. Alstadhaug KB. Migraine and the hypothalamus. *Cephalalgia* 2009; 29: 809–817.
10. Akerman S and Goadsby PJ. Dopamine and migraine: biology and clinical implications. *Cephalalgia* 2007; 27: 1308–1314.
11. Afridi SK, Kaube H and Goadsby PJ. Glyceryl trinitrate triggers premonitory symptoms in migraineurs. *Pain* 2004; 110: 675–680.
12. Maniyar FH, Sprenger T, Monteith T, et al. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain* 2014; 137: 232–241.
13. Cady RK, Voirin J, Farmer K, et al. Two center, randomized pilot study of migraine prophylaxis comparing paradigms using pre-emptive frovatriptan or daily topiramate: research and clinical implications. *Headache* 2012; 52: 749–764.
14. Luciani R, Carter D, Mannix L, et al. Prevention of migraine during prodrome with naratriptan. *Cephalalgia* 2000; 20: 122–126.
15. Kallela M, Wessman M and Farkkila M. Validation of a migraine-specific questionnaire for use in family studies. *Eur J Neurol* 2001; 8: 61–66.
16. Laurell K, Larsson B and Eeg-Olofsson O. Prevalence of headache in Swedish schoolchildren, with a focus on tension-type headache. *Cephalalgia* 2004; 24: 380–388.
17. Buse DC, Loder EW, Gorman JA, et al. Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: results of the American Migraine Prevalence and Prevention (AMPP) study. *Headache* 2013; 53: 1278–1299.
18. Lykke Thomsen L, Kirchmann Eriksen M, Faerch Romer S, et al. An epidemiological survey of hemiplegic migraine. *Cephalalgia* 2002; 22: 361–375.